REMARKS

Claims 1, 5-13, 19, 21-26, and 42-45 were pending in the subject application. By this Amendment, applicants have amended claims 1, 10-13, 42, and 44, added new claim 46, and canceled claims 5-9, 19, and 21-26 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future.

The amendments to claims 10-13 change the dependencies of these claims so that they no longer depend on canceled claims. The amendments to claims 1, 42 and 44 incorporate subject matter previously present in now canceled claims 8, 9, 24, and 26. Support for these amendments is found in the specification at, *inter alia*, page 14, lines 3-4 and lines 24-29; page 16, lines 27-31; page 17, lines 1-13 and lines 33-34. Support for new claim 46 may be found at page 14, lines 4-6. Applicants maintain that these amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 1, 10-13, and 42-45, each as amended, and new claim 46 will be pending and under examination.

Double Patenting Rejections

The Examiner maintained the rejection of claims 1, 5-13, 19, 21-26 and 42-45 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2 for reasons of record. The Examiner noted applicants had indicated they might consider filing a terminal disclaimer later in prosecution if allowable claims are indicated and the rejection is applicable thereto.

Rejections under 35 U.S.C. §103(a)

The Examiner maintained the rejection of claims 1, 5-13, 19, 21-26 and 42-45 under 35 U.S.C. §103(a) as allegedly unpatentable over Allaway et al. (U.S. Patent No. 5,817,767; herein, "Allaway") in view of Bolognesi et al. (U.S. Patent No. 5,464,933; herein, "Bolognesi"). As stated in the Office Action previously issued on February 9, 2005, the Examiner acnowledged that Allaway does not specifically mention the use of agents that bind epitopes of gp41 fusion intermediates, but that Allaway does teach the use of agents that bind to gp41 generally. The Examiner then alleged that the state of gp41, whether in its natural state or as a fusion intermediate, does not matter. The Examiner further alleged that one skilled in the art would have had a reasonable expectation of success that the use of Bolognesi's peptides in lieu of Allaway's agent would have interfered with gp41 fusion because both agents bind gp41, whether in the original state or in the fusion intermediate state. In the December 21, 2005 Office Action, the Examiner stated that applicant has amended the claims to recite that the composition comprises an admixture of two peptidyl compounds. The Examiner alleged that this embodiment of the claims falls under this rejection of record because the prior art teaches an admixture of two peptidyl compounds.

In response, applicants respectfully traverse this rejection.

Amended claims 1, 42 and 44 recite "a composition which comprises an admixture of two peptidyl compounds, wherein one compound is a monoclonal antibody or a portion thereof which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell and the other peptidyl compound is a peptide designated T-20 (SEQ ID

NO:1) which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate" (Emphasis added). Thus, the claimed invention provides the combination of (1) a monoclonal antibody which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell, and (2) T-20 which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate. This combination synergistically inhibits fusion of HIV-1 to CD4+ cells.

First, applicants maintain that Allaway et al. do not teach T-20, the second peptidyl compound now recited in claims 1, 42, and 44. Applicants further maintain that although Bolognesi et al. teach multiple peptides, one of which, a gp41 derived peptide (DP-178), corresponds to T20 of this invention (SEQ ID NO:1), Bolognesi does not provide any guidance to one skilled in the art as to the preference for T-20 in blocking fusion in combination with a monoclonal antibody which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell.

Second, applicants maintain that the combination of Allaway and Bolognesi does not provide any reasonable expectation of success that a composition comprising (1) a monoclonal antibody or portion thereof which retards binding of gp120 to CD4 on the surface of the CD4+ cell, and (2) T-20 (SEQ ID NO:1) which binds to an epitope on a gp41 fusion intermediate, would inhibit HIV-1 infection at all since the peptides employ different mechanisms for blocking fusion which could compete with one another, rather than work together, and certainly not that such a combination would do so synergistically when compared to the inhibitory effects of these two compounds individually.

As shown in Figures 1-3 of the subject application, the combined effect of these two peptidyl compounds is greater than an additive effect. As detailed in the specification at page 26, lines 8-10, the degree of synergy was quantified using the Combination Index (CI) method, wherein a CI value greater than 1 indicates antagonism, a CI equal to 1 indicates a purely additive effect, and CI less than 1 indicates a synergistic effect. As shown in Figure 2, potent synergies over broad ranges of inhibitor ratios and concentrations were observed with CI values as low as 0.20 under optimal conditions. These observed synergies translated into 17-fold and 5-fold reductions in the amounts of monoclonal antibody and T-20, respectively, needed to achieve 95% inhibition of viral entry, and even greater dose reductions were observed at higher levels of inhibition (see Figure 3). Applicants maintain that the observed synergy between these two peptidyl compounds was surprising and unexpected and therefore not obvious from Allaway and Bolognesi in combination.

In addition, applicants also maintain that the Examiner's conclusion that it would have been obvious to have substituted the peptides of Bolognesi et al. into the method of Allaway et al. and reasonably expected that the peptides would serve the same function as the agent of Allaway is not proper. Applicants maintain that the proper analysis is (i) whether one skilled in the art would have been motivated by the combined teachings of Allaway and Bolognesi to use the combination as claimed herein and (ii) whether one skilled in the art would have reasonably expected the synergistic effect from the combined teaching of Allaway and Bolognesi. Applicants maintain that the analysis is not simply whether the combination of Allaway and Bolognesi would produce an equivalent of applicant's composition. In this regard, applicants maintain that without the benefit of applicants' teachings in the instant application, one of ordinary skill in the art would not have been motivated to substitute the peptides of Bolognesi for the agents of Allaway, regardless of whether both of these compounds alone have the same function. Applicants maintain that the fact that two compounds are known to have the same function alone does not mean that these two compounds are interchangeable when used in combination with, for example, a monoclonal antibody which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell, as recited in claims 1, 42, and 44. As stated above, such compounds could have negative effects on each other. Therefore applicants maintain that one skilled in the art could not have even expected that the combination of these compounds would have additive effects, let alone that these compounds in combination would produce synergistic effects. Accordingly, applicants maintain that while the peptidyl compounds of the claimed method may have been separately known from these individual references, neither of the cited references teach the effect of combining a monoclonal antibody which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell, and T-20. In fact, this teaching is found only in the instant application. As described in the specification at page 27, lines 4-12, HIV-1 attachment and formation of gp41 fusion intermediates are inter-dependent steps. Therefore, HIV-1 attachment inhibitors administered in effective amount retard the binding of gp120 to CD4 but do not inhibit it completely. As a result, gp41 fusion intermediates are formed and persist for longer periods of time at levels below that required for membrane fusion and provide targets for inhibitory agents such as T-20. Accordingly, applicants maintain that in making this rejection, the Examiner relies on the teachings provided in the instant specification which show that not only does the combination not have adverse effects, but that when combined the two compounds actually produce unexpected improved results even beyond additive effects. Applicants maintain that such reliance on hindsight is not permissible when making a rejection under 35 U.S.C §103(a).

Lastly, on page 4 of the December 21, 2005 Office Action, the Examiner noted that the combination of CD4-IgG2 and T-20 is indeed synergistic in inhibiting HIV-1 infection at the points of viral fusion and entry. However, the Examiner maintained the rejection because this synergistic effect is allegedly limited to the CD4-IgG2 and T-20 combination and that the pending claims encompass other embodiments.

Applicants respectfully disagree with the Examiner's position. As stated above and described in the specification, HIV-1 attachment and formation of gp41 fusion intermediates are inter-dependent steps. Therefore, HIV-1 attachment inhibitors administered in effective amount retard the binding of gp120 to CD4 but do not inhibit it completely. As a result, gp41 fusion intermediates are formed and persist for longer periods of time at levels below that required for membrane fusion and provide targets for inhibitory agents such as T-20. Accordingly, applicants maintain that any monoclonal antibody which retards HIV-1 attachment when present in an effective amount which permits production of gp41 fusion intermediates will exhibit the same synergistic effect with T-20 as does CD4-IgG2. Thus, applicants maintain that the teaching of the synergistic effect exhibited by the composition comprising the instant peptidyl compounds renders the claimed invention unobvious over Allaway taken together with Bolognesi.

In view of the remarks above, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

Applicants respectfully submit that the grounds of rejection set forth in the December 21, 2005 Office Action have now been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw the grounds of rejection, and earnestly solicit allowance of all claims pending in the subject application, namely claims 1, 10-13, and 42-45, each as amended, and new claim 46.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $225.00 fee for a two-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

5/22/06

John P. White — Date
Reg. No. 28,678